Office Action Summary	Application No.	Applicant(s)	
	09/485,005	WANKER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/7/03 has been entered.

Amendment Entry

2. Applicant's amendment and response filed 4/7/03 in Paper No. 14 is acknowledged and has been entered. Claims 1, 6, 9, 13, 20, 21, 24, and 25 have been amended. Claim 26 has been added. Accordingly, claims 1-26 are pending and under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 102103

3. In light of Applicant's amendment and arguments, the rejection of claims 6-8 under 35 U.S.C. 102(b) as being anticipated by Tateishi et al (Membrane, 1993) is hereby, withdrawn.

4. In light of Applicant's amendment and arguments, the rejection of claims 4 and 17 under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Trottier (Nature, 1995) and in further view of Stott et al. (Proc. Natl. Acad. Sci. USA, 1995) is hereby, withdrawn.

5. In light of Applicant's amendment and arguments, the rejection of claims 13-14, 16, and 20 under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Smith (EP 0 293 249) and in further view of Stott et al. (Proc. Natl. Acad. Sci. USA, 1995) is hereby, withdrawn.

6. In light of Applicant's amendment and arguments, the rejection of claims 15 and 21-25 under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Smith (EP 0 293 249) and in further view of Stott et al. (Proc. Natl. Acad. Sci. USA, 1995) as applied to claims 13-14, 16, and 20 above, and further in view of Vitck et al. (US 5,935,927) is hereby, withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting, "contacting said filter with material of a sample suspected to comprise said fibrils or aggregates" because it is unclear what is encompassed by the term "material" as used in the claim and how it relates to the sample. It is specifically unclear how the filter is contacted with "a material" of the sample without contacting the rest of the sample itself. Please clarify.

Claim 9 is vague and indefinite in reciting, "contacting of said filter with material of a sample" because it is unclear what is encompassed by the term "material" as used in the claim and how it relates to the sample. It is specifically unclear how the filter is contacted with "a material" of the sample without contacting the rest of the sample itself. Please clarify.

Claim 12 is vague and indefinite in reciting, "said material of a sample" because it is unclear what is encompassed by the term "material" as used in the claim and how it relates to the sample. Please clarify.

Claim 18 is vague and indefinite in reciting, "dotting said material of the sample onto said filter" because it is unclear what is encompassed by the term "material" as used in the claim and how it relates to the sample. It is specifically unclear how the filter is dotted with "a material" of the sample without contacting the rest of the sample itself. Please clarify.

Claim 26 is vague and indefinite in reciting, "efficiency of the inhibitor" because the term "efficiency" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 5, 9-12, and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Tateishi et al (Membrane, 1993).

Tateishi et al. teach a method of detecting and removing detergent insoluble amyloid-like fibrils or protein aggregates (prion protein or PrPCJD) from the brain sample of mice with spongiform encephalopathy using a filter (virus removal membrane) which is cuprammonium regenerated cellulose hollow fiber (see Abstract and page 358, column 1). Filters for use in protein aggregate removal are commercially known with different mean pore sizes ranging from 35 nm to 75 nm (see page 358, column 2). Filtration is carried out under constant transmembrane pressure of 180 mmHg at 20 C. The existence of detergent insoluble amyloid-like fibrils or protein aggregates indicative of the neurodegenerative disease (agent infectivity) is confirmed by treatment with a detergent (surfactant), i.e. Sarkosyl, to solubilize the sample (see page 361, column 2). The presence of PrPCJD protein in the filtrate is detected immunohistchemically using a chemical reagent (see page 359, column 2).

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 4, 6-8, 17, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Kalchman et al. (US 6,235,879).

Tateishi et al. has been discussed supra.

Tateishi et al. differ from the instant invention in failing to teach using cellulose acetate membrane to filter the sample. Tateishi et al. differ from the instant invention in

failing to treat the sample specifically with sodium dodecyl sulphate or t-octylphenoxypolyethoxyethanol as detergent to solubilize proteins in the sample.

Kalchman et al. discussed the role of huntingtin and H1P1 in the pathology of Huntington's disease (HD) in column 2, lines 14-32 and column 5, lines 1-29. Kalchman et al. specifically disclose that the interaction between HD proteins and HIP1 is influenced by the number of polyglutamine repeats and that expanded polyglutamine tracts aggregate into large irregularly shaped deposits in HD brains. In protein preparation and western blotting for expressions studies, proteins were separated on sodium dodecyl sulphate (SDS-PAGE) mini-gels and HIP1 and huntingtin proteins were transferred and electroblotted on cellulose acetate membranes (PVDF membranes, Immobilon-P, Millipore). Immunoreactivity was determined using antibodies against HIP1 and Huntingtin and visualized in chemiluminescent ECL solution (see column 11, line 63 to column 12, line 20). Kalchman et al. further determined that HIP1 colocalized with Huntingtin in P2 and P3 membrane fractions and that solubilization with non-ionic detergent such as t-octylphenoxypolyethoxyethanol, i.e. Triton X-100 , revealed that HIP1 is insoluble to Triton X-100 (see Examples 7 and 8, especially column 11, lines 14-43). According to Kalchman et al., a variety of expression vectors can be transfected to express recombinant HIP modulating proteins or fragments in mammalian cells (see column 7, lines 10-55). Kalchman et al. observed that transfection of a gene encoding a fusion protein of 128 repeat Huntingtin and HIP1 (death effector domain) have resulted in aggregate formation in some cells in a cell culture.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Kalchman of polyglutamine expansions in proteins in Huntington's Disease, into the method of filtering and detecting insoluble amyloid-like fibrils or protein aggregates as taught by Tateishi because Kalchman specifically taught that neurodegenerative disorders associated with polyglutamine expansions such as Huntington's Disease involve aggregate formations of proteins that are insoluble even in detergents such as Triton X-100; thus, must be taken into consideration in the filtration method of Tateishi. One of ordinary skill in the art would have been motivated to incorporate the teaching of Kalchman into the method of Tateishi because protein aggregates that are insoluble to solubilization detergents such as Triton X-100 and which are retained in cellulose membranes after filtration in the method of Tateishi account for a percentage of proteins that necessitate isolation and detection for the determination of neurodegenerative diseases.

10. Claims 13, 14, 16, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993) in view of Kalchman et al. (US 6,235,879) and in further view of Smith (EP 0 293 249).

Tateishi et al. and Kalchman et al. have been discussed supra.

Tateishi et al. and Kalchman et al. differ from the instant invention in failing to teach the fusion protein as recited in claim 13.

Smith discloses a fusion protein in which a foreign protein or peptide is fused with an enzyme glutathione-S-transferase as well as expression vectors containing such

molecules (see Abstract and Summary). In column 4, Smith teaches that insolubility of glutathione-S-transferase fusion proteins is associated with the presence of strongly hydrophobic regions. Thus, insoluble fusion proteins can be purified by affinity chromatography using a solubilizing agent which does not disrupt binding to glutathione agarose such as Triton X-100.

(see column 4).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of the fusion protein by Smith into the method of Tateishi as modified by Kalchman in determining the presence of aggregate proteins indicative of neurodegenerative diseases because Smith specifically taught that certain fusion proteins fused with glutathione-S-transferase are rendered insoluble by strongly hydrophobic regions and Tateishi and Kalchman both taught application of their methods for capture and detection of insoluble protein aggregate forms including native or recombinant fusion proteins manifested in neurodegenerative diseases.

11. Claims 15, 21-23, and 26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al (Membrane, 1993 in view of Kalchman et al. (US 6,235,879), in further view of Smith (EP 0 293 249), and further in view of Vitck et al. (US 5,935,927).

Tateishi et al., Kalchman et al., and Smith have been discussed supra. Tateishi et al., Kalchman et al., and Smith differ from the instant invention in failing to disclose an inhibitor of amyloid-like fibril or protein aggregate formation.

Vitck et al. disclose that advanced glycosylation end-products (AGE)- amyloid polypeptides, i.e. AGE-β amyloid peptide (βAP), facilitate aggregation of amyloid fibrils in neurodegenerative diseases such as Alzeimer's disease (see column 5, lines 42-64, columns 9 and 11). Further, Vitck et al. disclose treatment of neurodegenerative disease using pharmaceutical compositions comprising inhibitors that prevent formation or cross-linking of AGE proteins resulting to amyloidosis and formation of amyloid fibrils (see columns 13-15).

One of ordinary skill in the art at the time of the instant invention would have been motivated to inhibit formation of amyloid fibrils in neurodegenerative diseases such as in the teaching of Tateishi as modified by Kalchman and Smith, using inhibitors in the form of pharmaceutical compositions such as taught by Vitck because Vitck specifically taught that such inhibitors prevent facilitated aggregation of amyloid fibrils in neurodegenerative diseases such as set forth in the claimed invention.

Response to Arguments

12. Applicant's arguments filed 4/7/03 have been fully considered but they are not persuasive.

A) Applicant argues the claims are not anticipated by Tateishi et al. Specifically, Applicant argues that in the claimed invention, the causative agent is rendered insoluble with detergent or urea whereas in Tateishi et al., use of sarkosyl renders the causative agent soluble. Specifically, Applicant contends that in the claimed invention the amyloid-like fibrils or protein aggregates in the sample are retained on the filter.

In response, claim 1 recites that the sample is "treated with detergent or urea to solubilize the sample" (to render the amyloid-like fibrils or protein aggregates insoluble) and that the sample is "filtered to capture the detergent or urea insoluble amyloid-like fibrils or protein aggregates" but fails to recite that the detergent or urea insoluble amyloid-like fibrils or protein aggregates are specifically captured or retained in the filter and not filtered through into the filtrate. It is noted that such feature upon which applicant relies is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Accordingly, the claims as currently recited read on the teaching of Tateishi et al.

13. For reason aforementioned, no claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Gailene R. Gabel
August 24, 2003